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Heterogeneity in presentation and treatment of catamenial anaphylaxis

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ABSTRACT

Background: Few reports have documented the uncommon association of the female menstrual cycle with anaphylaxis, an entity known as cyclic or catamenial anaphylaxis.
Objective: To examine cases of perimenstrual anaphylaxis, focusing on differences in presentation and response to treatment, in the hopes of enriching the description of this rare entity.
Methods: A cohort of 8 women with catamenial anaphylaxis were identified and retrospectively compared with regard to age at onset, organ involvement, diagnostic studies, and response to therapy.
Results: The median age at onset was 34 years (range, 14-40 years), and the median number of perimenstrual anaphylactic episodes at presentation was 10 per patient (range, 4-24 per patient). Most had cutaneous and gastrointestinal symptoms. The results of extensive investigations for anaphylactic triggers were negative, and masquerading conditions, such as carcinoid syndrome, pheochromocytoma, and systemic mastocytosis, were ruled out in all patients. Skin test results for progesterone were negative in all but 1 of 4 patients tested. None had elevated total serum IgE levels. Response to suppressive treatments regimens varied considerably, but none treated with high-dose systemic steroids had improvement. Similarly, ketotifen, celecoxib, rofecoxib, and oral contraceptives failed to control the anaphylactic reactions. Although antihistamines failed in 7 patients, 1 had improvement. Others responded to leuprolide, medroxyprogesterone, or salpingo-oophorectomy.
Conclusion: Whether the mechanism causing cyclical anaphylaxis may involve hypersensitivity to progesterone or prostaglandins, the variable response to suppressive medications in these cases suggests that catamenial anaphylaxis is a heterogeneous disorder in which a number of mechanisms and mediators may play a role. It is an emergent and probably underrecognized entity in the medical literature.

Introduction

Acute allergic reactions or exacerbations of preexisting chronic allergies in association with the female menstrual cycle are well documented for urticaria[1] and bronchial asthma.[2] Few reports have described the occurrence of anaphylaxis related to the menstrual period. In some cases, certain drugs used for menstrual cramps or foods taken around the time of menstruation have been implicated. However, in others, no obvious cause is seen despite exhaustive investigations. Catamenial anaphylaxis, also called cyclical anaphylaxis, describes recurrent episodes of multisystem allergic reactions occurring at the time of menstruation. We report results from a study of 8 patients with recurring, life-threatening perimenstrual allergic reactions. The demographics, natural history, and the response to treatment of this rare entity are described.

Methods

A multicenter study was performed from 1998 to 2011 to retrospectively collect and follow up all diagnosed cases of catamenial anaphylaxis. Three academic centers were involved, and appropriate institutional review board approvals were obtained (Children's Hospital of Wisconsin, St. Michael's Hospital, and Hamilton Health Sciences Centre). Patients were selected on the basis of the following criteria: (1) recurrent anaphylactic episodes[3]; (2) absence of identifiable triggers, such as food, drug, or exercise; and (3) perimenstrual timing of the anaphylactic reactions. For inclusion, at least one of the perimenstrual episodes must have occurred during the late luteal or early follicular phase of the menstrual cycle (days 26 to 3), with all episodes analyzed occurring within days 22 to 7 of the menstrual cycle.[2,4] Eight women met

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these inclusion criteria, and age at onset, organ involvement, diagnostic studies, and response to therapy were documented.

Results

Case 1

A 38-year-old woman first presented in February 2002 with a 2-year history of episodic reactions that occurred temporally in relation to her menstrual period. At the time of consultation, she had had a total of 24 such reactions. Manifestations included a "draining sensation" in the chest followed by pruritus of the palms and heart palpitations. Subsequently, she developed crampy abdominal pain, diarrhea, lightheadedness, and, on approximately 13 occasions, loss of consciousness. During only some reactions, she experienced flushing, urticaria, and chest tightness. Systolic blood pressure was documented to be as low as 70 to 80 mm Hg by paramedics on several occasions.

All of these episodes were perimenstrual, starting either the day before, the day of, or the day after the onset of menses. Episodes were not related to food, exercise, alcohol, or use of any medication. Medical history was significant only for hypothyroidism, for which she was undergoing replacement therapy. Details of the reactions and investigations performed on this patient are given in Table 1 and Table 2, respectively. Of note, the result of intradermal skin testing of 0.03 mL of medroxyprogesterone was positive at a concentration of 1.5 mg/mL.[5–7]

She was prescribed cetirizine, 10 mg/d, and prednisone, 60 mg/d, for 1 week then every other day. No improvements were seen. Prednisone therapy was eventually discontinued, and the cetirizine dosage was increased to 20 mg/d with near-total suppression of reactions. Follow-up for a period of 1 year with cetirizine, 20 mg/d, revealed occurrence of only one mild reaction.

Case 2

A 33-year-old woman was first seen in April 1998 with an 18-month history of recurrent anaphylactic reactions. Her first reaction occurred in October 1996 with generalized flushing, facial and oropharyngeal pruritus, facial angioedema, and uterine cramps. There was associated nausea, vomiting, diarrhea, and a sensation of lightheadedness and presyncope. The second reaction happened several months later but was more severe, involving respiratory symptoms, syncope, and hypotension documented by paramedics. By the time she was seen in consultation, she had experienced a total of 12 such reactions, with 10 of them coinciding with her menstrual period (the other 2 were in the middle of her cycle). She was not taking any medications at the time of the reactions, and the reactions were not associated with any food, alcohol, or exercise. Details of the reactions and investigations performed on this patient are listed in Table 1 and Table 2, respectively.

Initially, she was treated with a suppressive regimen for idiopathic anaphylaxis using prednisone at a daily dose of 50 mg orally. This treatment failed to suppress her reactions. Prophylactic treatment with cetirizine, 10 mg twice daily, in combination with ketotifen, 4 mg twice daily, also failed to control her symptoms. Celecoxib, a selective cyclooxygenase 2 (COX-2) inhibitor, was tried but caused episodes of angioedema. Finally, leuprolide, a luteinizing hormone–releasing hormone agonist, was prescribed; no recurrence of her symptoms occurred during a 1-year follow-up period.

Case 3

A 29-year-old woman was initially seen in August 1999 with a 2-year history of recurrent episodes of chest pain; generalized urticaria; swelling of her face, lips, and neck; cough; vomiting; crampy abdominal pain; and dizziness and lightheadedness. These reactions started approximately 1 week before the beginning of each menstrual cycle. Symptoms worsened during the week and peaked on the first day of her menstrual cycle. At the time of her initial evaluation, she had had a total of 12 such reactions, none of which was associated with food, alcohol, or exercise. At the time of her first visit, she was taking rofecoxib with no change in the frequency or severity of her attacks. Her medical history was significant for fibromyalgia for which she was taking daily acetaminophen with codeine. Details of the reactions and results of

Table 1
Patient characteristics and details of their reactions

Patient details	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age at onset of symptoms, y	36	31	27	40	36	28	40	14
Age at presentation, y	38	33	29	40	37	32	43	17
No. of prior anaphylactic episodes that coincided with the menstrual cycle at presentation	24	10	12	4	ND	7	6	12
Anaphylactic episodes associated with the menstrual cycle, %	100	83	100	67	100	15	67	100
Day of menstrual cycle at which anaphylactic symptoms peaked (range when applicable)[a]	28 to 2	26	28 to 2	1 to 3	1 to 7	22 to 2	1 to 2	1 to 7
Organ involvement, %								
Cutaneous	100	100	100	100	100	100	83	100
Pulmonary	0	50	100	33	100	0	83	100
Gastrointestinal	100	100	100	100	0	100	0	100
Cardiovascular and neurologic	50	100	100	33	0	100	0	100
Medications or interventions that suppressed or attenuated reactions	Cetirizine	Leuprolide	Medroxyprogesterone	Leuprolide Bilateral salpingo-oophorectomy	NA	NA	Bilateral salpingo-oophorectomy	NA
Medications or interventions that worsened or failed to improve reactions	Prednisone	Prednisone Cetirizine Ketotifen Celecoxib	Cetirizine Prednisone Rofecoxib	Cetirizine Montelukast Ketotifen Prednisone	OCP Pregnancy Diphenhydramine Cetirizine	Diphenhydramine	Prednisone Diphenhydramine	Cetirizine

Abbreviations: NA, not applicable; ND, no data; OCP, oral contraceptive.
[a]Day 1 is defined as the onset of menses; day 28 is the day before menses.

Table 2
Results of investigations performed in the 8 patients

Investigation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Skin test to medroxyprogesterone[a]	Negative	Negative	Negative	ND	ND	Positive[b]	ND	ND
Total serum IgE[c]	Normal	Normal	Normal	ND	ND	ND	Normal	Normal
Serum tryptase at baseline[d]	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Serum tryptase during anaphylaxis[d,e]	ND	46.9 ng/mL	ND	ND	ND	ND	Normal	ND
24-Hour urine for 5-HIAA	Negative	Negative	Negative	Negative	ND	ND	Negative	Negative
24-Hour urine for VMA	Negative	Negative	Negative	Negative	ND	ND	Negative	Negative
24-Hour urine for catecholamine	Negative	Negative	Negative	Negative	ND	ND	Negative	Negative

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; ND, no data; VMA, vanillylmandelic acid.
[a]Performed by intradermal injection of 10 mg/mL (0.03 mL) of medroxyprogesterone.
[b]Positive to intradermal testing with medroxyprogesterone at concentration of 1.5 mg/mL.
[c]Reference range is less than 300 IU/mL.
[d]Reference range is 3.8 to 11.4 ng/mL.
[e]During a reaction was defined as within 3 hours of symptom onset.

investigations performed on this patient are listed in Table 1 and Table 2, respectively.

Initially, starting 3 days before menstruation and continuing until 2 days after the onset of menstruation, she was treated with cetirizine, 10 mg twice daily, and prednisone, 40 mg daily. This failed to suppress her reactions. Later, unknowingly to her allergists, she was prescribed medroxyprogesterone acetate for contraception by her primary care physician. In the ensuing 3 years, she had total suppression of her multisystem reactions.

In November 2003, medroxyprogesterone therapy was stopped because she wanted to become pregnant. Three months later, she had a recurrence of her anaphylactic symptoms. Although initially mild, her symptoms worsened during several months and included lip swelling, throat constriction, dysphonia, dysphagia, chest tightness, wheezing, and presyncope. Because of these life-threatening manifestations, medroxyprogesterone therapy was restarted, and cessations of symptoms ensued during a follow-up period of 2 years.

Case 4

A 40-year-old woman presented in May 2007 with a 3-month history of 6 recurrent episodes of crampy abdominal pain, diarrhea, vomiting, generalized urticaria, swelling of the face and neck, and sensation of throat constriction. On 2 occasions, she also had associated cough, chest tightness, dyspnea, and presyncope. At least 4 of her 6 reactions were perimenstrual, and the reactions were not associated with any specific foods, exercise, or medication. Her medical history was significant for thyroid goiter and childhood asthma. Details of the reactions and results of investigations performed on this patient are listed in Table 1 and Table 2, respectively.

Trials of cetirizine, 20 mg twice daily, montelukast, 10 mg daily, ketotifen, 2 mg twice daily, and prednisone, 50 mg daily, failed. She was then treated with leuprolide and had complete suppression of her reactions. Because the patient was having a hysterectomy for a prolapsed uterus, she opted to also undergo bilateral oophorectomy. She has had continued suppression of her reactions since the surgery to date.

Case 5

In August 2007, a 37-year-old woman presented with multiple episodes of urticaria and angioedema. This had begun after she became pregnant, in March 2006. Concomitant symptoms included nasal congestion, postnasal drip, inspiratory stridor, productive cough, and dysphagia without the sensation of throat constriction. After an uneventful delivery in November 2006, she continued to have reactions post partum. These began 1 week before her menstrual periods but peaked with menstruation and were not related to food, drug, or activity. Her medical history was significant for eczema and drug allergy (oral contraceptives caused urticaria). Details of the reactions and results of investigations performed on this patient are listed in Table 1 and Table 2, respectively.

She was first treated with antihistamines. Both diphenhydramine and cetirizine failed to diminish the severity of her reactions. Unfortunately, she was thereafter lost to follow-up.

Case 6

A 32-year-old woman presented in October 2010 with a 4-year history of recurrent episodes of generalized urticaria, swelling of her lips and face, palpitations, severe crampy abdominal pain, and lightheadedness without loss of consciousness. She had had a total of 7 such reactions in 47 menstrual cycles, all of which developed within 1 week of or immediately after her menstrual period. Her reactions were not associated with any specific foods, medications, or exercise. Her medical history was remarkable for eczema and dermatographism. Details of the reactions and investigations performed on this patient are listed in Table 1 and Table 2, respectively.

At this point, a trial of diphenhydramine had already failed to suppressed her reactions. On the basis of her positive medroxyprogesterone skin test result, interruption of the menstrual cycle with leuprolide was offered. The patient declined this. A trial of cetirizine and ketotifen was also offered, but the patient opted to forgo all treatment because of the infrequency of her reactions.

Case 7

A 43-year-old woman with menopausal symptoms since January 2008 and irregular menstrual periods presented with 9 episodes of anaphylaxis, beginning in November 2008. The latter 6 episodes correlated with her menstrual cycle, usually occurring within 48 hours of menstruation. No other etiologic agent could be identified, including food, drug, and exercise. Menstrual dates were not available for the first 3 episodes of anaphylaxis, and all were accredited to possible food allergies. Her menstrual-associated anaphylactic reactions were severe,[8] with 1 requiring intubation and 2, after epinephrine failed, requiring methylene blue infusion.[9] Her medical history was notable for allergic rhinitis with oral allergy syndrome, peanut allergy, cerebrovascular disease, migraine disorder, multiple drug allergies, and acid reflux disease. Details of the reactions and investigations performed on this patient are listed in Table 1 and Table 2, respectively. In addition, bone marrow biopsy findings were unremarkable (including being negative for the KIT D816V mutation and the other features diagnostic of mast cell disorders), and the platelet-activating factor acetyl-hydrolase level was normal.[10]

Prophylactic corticosteroids and antihistamines were implemented and, during a 4-month interval, only one menstrual period was without anaphylaxis. Because of history of a cerebrovascular accident, hormonal therapy was not attempted. The patient ultimately underwent total laparoscopic hysterectomy and bilateral

salpingo-oophorectomy. In the subsequent 8 months, she had remission of catamenial anaphylaxis.

Case 8

An otherwise healthy, 17-year-old girl presented in April 2012 with 12 systemic reactions that coincided with every menstrual period she had since April 2012. Symptoms included widespread urticaria; facial erythema, warmth, and angioedema; conjunctival injection; dyspnea, cough, stridor, and expiratory wheeze; nausea, diarrhea, and abdominal pain; dysphagia; and presyncope without loss consciousness. Reactions occurred within the first week of menses. The paramedics were called on 10 of the 12 occasions, during which she was found to be hypotensive and treated with epinephrine by autoinjector. Further details of the reactions and investigations performed on this patient are listed in Table 1 and Table 2, respectively.

A 3-month trial of cetirizine, 20 mg daily, failed because she had 3 further perimenstrual reactions. She was then prescribed an oral contraceptive. She has not been followed up since.

Discussion

Catamenial anaphylaxis is an uncommon clinical entity with few reports in the medical literature describing such reactions.[4,7,11–18] It is a diagnosis of exclusion that requires ruling out allergic reactions related to medications, especially acetylsalicylic acid and nonsteroidal anti-inflammatory drugs,[19] foods, and other triggers, and conditions that mimic anaphylaxis, such as carcinoid syndrome, pheochromocytoma, and systemic mastocytosis.[20]

On excluding extrinsic triggers of anaphylaxis and conditions that mimic multisystem allergic reactions, the diagnosis of catamenial anaphylaxis should be considered. The mechanism involved in catamenial anaphylaxis is not clearly understood. Some authors have suggested hypersensitivity to progesterone as an underlying cause.[15] This theory was supported in some patients by a positive cutaneous and systemic reaction to intradermal challenge with medroxyprogesterone,[15] with the former being observed in one of our patients. However, in a report of 4 patients with similar cyclical anaphylactic reactions, 2 did not have positive skin test results to medroxyprogesterone.[4] A similar negative skin test result was also seen in one other patient,[13] as well as in 3 of our 4 patients tested, although the positive and negative predictive values for such unstandardized skin tests are unknown. We did not perform progesterone challenge in our 3 patients with negative medroxyprogesterone skin test results. Although serum progesterone specific IgE and basophil histamine release with progesterone were observed in a patient who had anaphylaxis to exogenous progesterone,[21] these studies have not been performed in catamenial anaphylaxis patients.[17] Clearly, this phenomenon cannot account for all cases of cyclical anaphylaxis. Furthermore, the use of depot preparations of progesterone would likely exacerbate the condition in patients allergic to endogenous progesterone, in contrast to case 3 described above.

Our fifth patient had a history of reactions to birth control pills, suggestive of hypersensitivity to both exogenous and endogenous progesterone. She also developed her first manifestations during pregnancy, with later premenstrual recurrences. This finding may suggest first sensitization to exogenous progesterone followed with resensitization to the high levels of endogenous progesterone during pregnancy. Alteration of immune responses during pregnancy may also play a part in the pathogenesis.[18]

Another mechanism proposed to account for catamenial anaphylaxis involves a vasoactive constituent of menstrual fluid, the prostaglandins.[11,13,16] This was supported by the finding that prostaglandin $F_{2\alpha}$ plays an important role in modulating mediator release in mast cells.[22] Prostaglandin I_2 (prostacyclin) is a powerful vasodilator and may lead to systemic reactions in susceptible persons.[11] This theory was supported by a positive intradermal skin test result to menstrual fluid in one[11] but not another patient.[16]

Our patients had a median age at onset of 34 years (range, 14-40 years), with a 1.5-year delay in seeking consultation with an allergist. The median number of perimenstrual anaphylactic episodes at presentation was 10 per patient (range, 4-24 per patient), and the median frequency of menstrual cycles coinciding with anaphylactic episodes was 92% (range, 15%-100%). All patients resided in the Northern hemisphere, either Wisconsin or Canada. The most frequent symptoms were cutaneous, followed by gastrointestinal, cardiovascular or neurologic, and pulmonary (Table 1). The results of extensive investigations for anaphylactic triggers, including foods and medications, were negative in all patients presented in this report. Many patients were atopic however, with 2 having drug allergy and 1 having food allergy. Conditions that can masquerade as anaphylaxis, such as carcinoid syndrome, pheochromocytoma, and systemic mastocytosis, were ruled out by history, manifestations during the multisystem reactions, and appropriate laboratory tests. None had elevated total serum IgE levels.

The treatment of these patients represents a spectrum of therapeutic modalities. For the first patient, cetirizine, 10 mg daily, did not control her symptoms. Rather, increasing the dose of cetirizine to 20 mg/d surprisingly did. In contrast, all the other patients did not respond to antihistamines. In the second patient described here, a trial of celecoxib was unsuccessful in preventing her reactions and, in fact, provoked angioedema. In the third patient, rofecoxib similarly failed to suppress the reactions. This is in contrast to reports by Simpson et al[16] and Burnstein et al[13] in which their patients improved after the initiation of celecoxib and indomethacin, respectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common drugs known to precipitate anaphylaxis and other allergic reactions.[20] There is also compelling evidence that NSAIDs and aspirin can intensify immediate hypersensitivity reactions in patients with background of anaphylaxis.[23,24] Also, NSAIDs have been found in vitro to augment histamine release from human leukocytes.[25] The same is true for COX-2 inhibitors, with anaphylactic reactions related to such medications.[26,27] The role of COX inhibitors in catamenial anaphylaxis remains unclear at this time.

Successful treatment occurred in the second and fourth patients with an luteinizing hormone–releasing hormone analog, a finding also seen in 2 of 4 patients seen by Slater et al.[4] In the third patient, complete suppression of her episodes of anaphylaxis ensued on initiation of medroxyprogesterone therapy. Such therapy was tried, to our knowledge, in only one other patient and failed to control her symptoms.[16] In the literature, 2 catamenial anaphylaxis patients were successfully treated with oral conjugated estrogen.[12,14] However, such long-term therapy may be associated with risk, namely, malignant tumors. Progesterone desensitization was recently reported to be another successful treatment option in infertile women with hypersensitivity reactions to exogenous progesterone.[28] In patients with severe life-threatening symptoms refractory or intolerant to medical treatments, surgical castration with a total abdominal hysterectomy and bilateral oophorectomies was reported to be the definitive treatment,[18] as was opted for by the fourth patient and required in the seventh patient (who could not receive hormonal therapy due to history of cerebrovascular accident).

High-dose systemic steroids failed to control the anaphylactic reactions in all those treated with them, despite the fact that this approach is recommended for the control of idiopathic anaphylaxis.[29,30] In addition, we found that ketotifen, a mast cell stabilizer with antihistaminic activity, did not help to reduce the frequency or severity of attacks in the second and fourth patients, despite its reported efficacy in the treatment of idiopathic anaphylaxis.[31] Clearly, catamenial anaphylaxis must be distinguished from idiopathic anaphylaxis because of its distinctive treatment.

This study investigates a sizable cohort of patients with catamenial anaphylaxis. Nonetheless, a limitation to this study remains its small sample size. Furthermore, although much can be gleaned with regard to presentation and response to treatment in this primarily retrospective study, an investigation that is prospective and masked to treatment interventions would yield even more valuable information. Clearly, future studies need to be undertaken to better understand the relationship between the menstrual cycle and anaphylaxis, especially with regard to treatment options given the variable response to different therapeutic modalities seen here.

Whether the mechanism that causes cyclical anaphylaxis involves hypersensitivity to progesterone or prostaglandins, cessation of the menstrual cycle by means of induction of medical or surgical menopause reportedly results in control of most such anaphylactic reactions.[4,11,15] The variable response to suppressive medications and the unpredictable presentations among the patients described here suggest that catamenial anaphylaxis is a heterogeneous disorder in which a number of mechanisms and mediators likely play a role. At this time, the optimal treatment approach, which is distinct from that of idiopathic anaphylaxis, remains somewhat unclear.

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